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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/232,290	01/15/99	PLUCKTHUN	A MORPHO/7

HM22/1205

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EXAMINER	
DECLOUX, A	
ART UNIT	**PAPER NUMBER**
1644	18

DATE MAILED: 12/05/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/232,290	Pluckthun, A et al.
Examiner	**Group Art Unit**
DeCloux, Amy	1644

☒ Responsive to communication(s) filed on *mailed on 9-19-00*

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-27* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-27* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☒ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Applicant's amendment, mailed 9-22-00 (Paper No. 16)is acknowledged.

2. The rejections of record can be found In the previous Office Action mailed 6-19-00 (Paper No. 15). In view of applicant's amendment mailed 9-22-00 (Paper No. 16) , the objections to the specification in paragraphs 4-6 have been withdrawn as have the 112 2nd rejections. Also in view of the receipt of the certified copy of EP96 11 1441.0 filed 7-19-96, the 102 (a) rejection has been withdrawn. However the 102(b) and 103(a) rejections are maintained.

3. In view of applicant's amendment and arguments the 112 1st paragraph rejection has been withdrawn with respect to claims 8, 9, 11, which encompass sequences encoding antibody derived molecules, but is maintained with regard to claims 1-7 and 13-27. Applicant argues that the instant specification discloses three different modifications to Fab and Fv fragments that increase solubility and that it would not be reasonable to provide similar details on every DNA sequence of the present invention. Examiner agrees but notes that the examples are on antibody derived molecules and not on any other type of immunoglobulin superfamily member which have distinctly different structures, properties and functions from antibody members as discussed in the 112 1st rejection of the previous office action which is modified below. Therefore, the applicant's arguements have been carefully considered but are not deemed persuasive..

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims **1-7 and 13-27** are rejected under *35 U.S.C. 112*, first paragraph, because the specification, while being enabling for a DNA sequence comprising a sequence that encodes a modified scFv fragment with mutations in the conserved framework as recited in claim 10 and in claim 12 as it pertains to scFv Fab fragment, an Fv fragment, and an Fv fragment stabilized by an inter-domain disulphide bond as recited in claims 8, 9 and 11, respectively, does not reasonably provide enablement for any DNA sequence modified to encode and confer increased hydrophiliicity in the interface wherein said sequence encodes a modified DNA sequence encoding <u>any</u> modified immunoglobulin superfamily domain or fragment as recited in Claim 1 and its dependent claims with the exception of dependent claims 8 - 12 as it pertains to antibody derived molecules. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Factors to be considered in

determining whether undue experimentation is required are summarized in *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, unpredictability in the art, the amount of experimentation required, and the amount of direction or guidance presented.

With the exception of the disclosure of a modified scFv fragment with mutations in the conserved framework , no sequence data regarding a modification conferring increased hydrophilicty of any DNA sequence comprising a DNA sequence encoding any modified immunoglobulin superfamily domain or fragment, as recited in Claim 1, is found within the specification. There are no DNA sequences provided that encode modifications conferring increased hydrophilicty of any member of the immunoglobulin gene superfamily (with the exception of the disclosure of a modified scFv fragment) which consists of molecules with immunoglobulin-like domains. Members of this superfamily include class I and class II major histocompatibility antigens, immunoglobulins, T-cell receptor alpha, beta, gamma and delta chains, CD1, CD2, CD4, CD8, CD28, the gamma, delta and epsilon chains of CD3, OX-2, Thy-1, the intercellular or neural cell adhesion molecules (I-CAM or N-CAM), lymphocyte function associated antigen-3 (LFA-3), neurocytoplasmic protein (NCP-3), poly-Ig receptor, myelin-associated glycoprotein (MAG), high affinity IgE receptor, the major glycoprotein of peripheral myelin (Po), platelet derived growth factor receptor, colony stimulating factor-1 receptor, macrophage Fc receptor, Fc gamma receptors and carcinoembryonic antigen as taught by Capon et al in U.S. Patent 5,514,582 in Column 1, lines 30-44.

It is not sufficient to define a DNA sequence by its principal biological activity, IE a DNA sequence capable of encoding a modified immunoglobulin superfamily domain with increased hydrophilicity in the interface region, especially in view of the lack of knowledge of the exact identity of which amino acid changes would confer increased hydrophilicity and still function otherwise likewise to its parent molecule as evidenced by Nieba et al (1997) in Protein Engineering 10(4):435-444, (see entire article, especially page 435, column 2, second from the last paragraph) where it is taught that there is limited understanding of how specific sequence modifications in those parts of the antibody molecule which are not directly involved in antigen recognition can change the properties of recombinant Fv and scFv. Accordingly this same paucity of understanding can be applied to the unknown effect on the molecule's original properties upon modification of domains of members of any immunoglobulin superfamily, including an Fab fragment, an Fv fragment and an Fv fragment stabilized by an interdomain di-sulphide bond as encompassed in the instant claims. Due to the different secondary structure of antibody derived fragments compared to other members of the immunoglobulin superfamily, modifications in certain residues of an scFv fragments as disclosed in the instant specification would not be reasonably expectd to have the same effect as identical modifications in other members of the immunoglobulin superfamily, absence evidence to the contrary, in view of the distinct antibody structure compared to other immunoglobulin superfamily members, because the problem of predicting functional aspects of the product from mere sequence data and what changes can be

tolerated is complex and well outside the realm of routine experimentation. *In re Fisher*, 1666 USPQ 19 24 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Without such guidance, the DNA sequences encoding for modifications conferring increased hydrophilicity in an interface region in an immunoglobulin superfamily domain fragments and still maintain the properties that define the molecule as an immunoglobulin superfamily member is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly extensive and undue. See *Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd.*, 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) at 18 USPQ2d 1026-1027 and *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). Therefore, there is no evidence of record to show that one skilled in the art would be able to practice the invention as claimed without an undue amount of experimentation.

In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take undue trials and errors to practice the claimed invention and this is not sanctioned by the statute.

6. With regard to the outstanding 102(b) and 103 rejections, applicant argues that the definition of "interface" used by Johnson et al is different from that of the instant specification because the VL VH interface in Johnson is not between "contiguously adjoined" domains as recited in applicant's amended claim 1 but instead exists between distinct polypeptides. However, the examiner notes that Johnson also teaches said alterations in contiguously adjoined domains such as those found in single chains antibodies in which the VL and VH domains are recombinantly joined contiguously, as discussed in the previous office action which is repeated below for the appliant's convenience. Therefore, although applicant's arguments have been carefully considered, they are deemed unpersuasive and the 102(b) and 103(a) rejections are maintained.

7. The following is a quotation of the appropriate paragraphs of *35 U.S.C. § 102* that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1-7, 10, 13-17, and 26-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Johnson et al (WO 92/01787)(IDS).

Johnson et al teach an analogue of a single chain variable domain of a member of an immunoglobulin or immunoglobulin superfamily, in which said analogue one or more interface amino acid residues of the domain is altered, wherein the said altered amino acid is substituted with a residue so that the analog is more hydrophilic than the

unaltered domain, (see entire patent, especially pages 6 and 7, last and first paragraph, respectively) and teaches that said analogues are obtained using site directed mutagenesis and a recombinant expression system, (see entire patent, especially pages 9-10) as recited in Claims 1 and 26-27. Johnson et al teach that said analogues comprising domains which are synthetic analogs of a natural single variable domain of a member of an immunoglobulin superfamily (see entire patent, especially page 1, lines 6-9) such as single chain variable domains (see entire patent, especially page 19). With regard to claims 2-7 and 10, Johnson et al teach that said alteration of a single chain variable domain of a member of an immunoglobulin or immunoglobulin superfamily may be by way of amino acid substitution, deletion, addition inversion, (see entire article, especially page 7, lines 12-15) and the amino acids substituted include Q, T E D S G or N (see entire patent, especially pages 7 and 8). With regard to claims 13-14, Johnson et al teach said single chain moieties may be further coupled an additional moiety that can be enzymic, florescent, radiolabeled or a portion of an immunoglobulin (see entire patent, especially page 8, lines 17-21). With regard to claims 15-17, Johnson et al also teaches cloning the recombinant products into fd phage (see entire patent, especially page 20 , line 1) and also that said analog or derivative can be displayed on a phage as a fusion with gene III protein of filamentous bacteriophage (see entire patent, especially page 20 , lines 15-23).

Therefore, the reference teachings anticipate the claimed invention

9. The following is a quotation of *35 U.S.C. § 103* which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under *subsection (f) or (g)* of *section 102* of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 1-7, 10, 13-17, 18-22, and 26-27 are rejected under 35 U.S.C. 103(a) as

being unpatentable over Johnson et al (WO 92/01787)(IDS) in view of Jenkins et al (PNAS 92:6057-6061, 1995)(IDS) and Knappik et al (Biotechniques 17(4):754-761, 1994)

Johnson et al teaches as above, however Johnson et al does not teach a DNA sequence with an additional moiety capable of binding a metal ion, as recited in claims 18-19, or a peptide or labeling tag moiety as recited in claims 20-22.

Jensen et al teaches DNA recombinant methods of producing mutants of the HIV integrase gene by replacing hydrophobic residues to increase its solubility (see page 6060, column 2, third paragraph of Discussion section). Jensen et al also teaches that the recombinant methods include the use of a histidine tag that allows rapid purification of the expressed protein on a nickel chelating column (see entire article, especially page 6057, column 2, last paragraph).

Knappik et al teaches that the FLAG peptide has been successfully used as a detection and purification tag of antibody fragments expressed in E. Coli (see entire article, especially page 761, column 1, first sentence).

Therefore, it would have been obvious to one of skill in the art at the time the invention was made to have made and used a DNA sequence as recited in Claims 1-7, 10, 13-17, and 26-27 in view of the teachings of Johnson et al. for the reasons stated in the above 102b rejection in Section 11 of this office action.

With regard to claims 18-22, it would have been obvious to one of skill in the art at the time the invention was made to have made and used a DNA sequence as taught by Johnson et al that had an additional moiety of a histidine tag as taught by Jensen et al, or an additional moiety of a FLAG peptide as taught by Knappik et al because both Jensen et al and Knappik et al teach that said moieties aid in the detection and purification of expressed proteins, especially antibody fragments, and one would expect that it would also aid in the detection of recombinant mutants of said antibody fragments.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

12. The following are new ground of rejection based on the amendments to the instant claims.

13. A) Claims 1 and dependent claims 2-27 are rejected under 35 U.S.C. 112, first

paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Newly added claim 1 has been amended to recite that the IGSF encoded by the claimed DNA sequence would retain the ability to bind antigen and is not supported by the specification or by the claims as originally filed. There is no support in the specification or claims as originally filed for the recitation " domain or fragment retains the ability to bind antigen". Applicant asserts that support is found on page 22, line 30-page 23, line 5. There is no written description of the claimed invention in the specification or claims as originally filed. Thus the claimed invention constitutes **new matter.** Applicant is invited to directly quote the text of support in the specification.

B) Claims 1 and dependent claims 2-27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Newly added claim 1 has been amended to recite that an interface with a second domain contiguously adjoined to said parent IgSF domain, and is not supported by the specification or by the claims as originally filed. There is no support in the specification or claims as originally filed for the recitation "contiguously". Applicant asserts that support is found on page 5, lines 1-4, however there is no mention that the interface of the disclosed domains are contiguous. There is no written description of the claimed invention in the specification or claims as originally filed. Thus the claimed invention constitutes **new matter.** Applicant is invited to directly quote the text of support in the specification.

14. The amendment filed is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: on page 10, lines 26-29:--By engineering one or more fused additional domains as association domains, IgSF domains or fragments can be assembled into larger molecules which also fall under the scope of this invention--, and on page 10, line 29 --The term association domain may refer to a domain which results in self association of two or more antibody fragmetns of the present invention. An association domain could be derived, for example, from a leucine zipper o from a helix-turn-helix motif. Furthermore, the term association domain may refer to domains which result in hetero-association of two or more antibody fragments of the present invention. For example, the fused additional moiety may comprise a first association domain which results in heteroassociation of one or more antibody fragments of the present invention with one or more peptides or protiens comprising a second heteroassociation domain being able to associate with said first hetero-association domain.--..

Applicant is required to cancel the new matter in the reply to this Office action.

15. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy DeCloux whose telephone number is (703) 306-5821. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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Dec. 4, 2000

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